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Solvent-free synthesis of α-aminonitriles from aldehydes, amines and trimethylsilyl cyanide catalyzed by thallium(III) chloride tetrahydrate

Anjoy Majhi, Sung Soo Kim* and Santosh T. Kadam

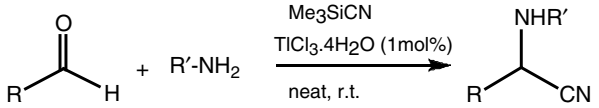
A straightforward and efficient method has been developed for the synthesis of α-aminonitriles by combining aldehydes, amines and trimethylsilyl cyanide in the presence of a catalytic amount of thallium(III) chloride tetrahydrate (1 mol%) under solvent-free conditions at room temperature.

Keywords: three-component coupling reaction; thallium(III) chloride tetrahydrate; aldehydes; amines; trimethylsilyl cyanide; α-aminonitriles; solvent-free

Introduction

α-Aminonitriles are important intermediates for the preparation of many amino acids[1] and various nitrogen containing heterocycles such as imidazoles and thiadiazoles, etc.[2] α-Amino acids, in turn, are of great biological and economical importance due to their significance in chemistry and biology and as useful chiral building blocks.[3–7] The Strecker reaction is one of the most efficient and straightforward methods for the synthesis of α-aminonitriles.[8] The classical Strecker reaction is generally carried out by the nucleophilic addition of cyanide ion to the imines using various Lewis acid or Lewis base catalysts.[9–12] Subsequently, several modifications of the Strecker reaction have been reported using a variety of cyanating agents such as α-trimethylsiloxynitriles and diethylphosphorocyanidate under various reaction conditions.[13,14] The use of TMSCN is a safer and more effective cyanide anion source for the nucleophilic addition reactions compared with hydrogen cyanide, sodium cyanide or potassium cyanide.

Recently numerous methods have been developed for the synthesis of α-aminonitriles from aldehydes, amines and TMSCN or tributyltincyanide catalyzed by Lewis acids such as lithium perchlorate, polymeric scandium triflamide, vanadyl triflate, $NiCl_2$, $BiCl_3$, zinc halides, $RuCl_3$, ytterbium triflate, montmorillonite, iodine, (bromodimethyl)sulfonium bromide and $La(NO_3)_3{\cdot}6H_2O$ or $GdCl_3{\cdot}6H_2O$.[15–26] There have also been a few reports using no catalyst.[27–29] However, their reaction time was in the range of hours. Solid catalysts such as heteropoly acids[30] and guanidine hydrochloride[31] have been employed for the synthesis of α-aminonitriles. Most recently a method utilizing 5 mol% $Fe(Cp)_2PF_6$ was reported for the synthesis of α-aminonitriles of ketones and aldehydes.[32] However, many methods involve the use of strong acidic conditions, extended reaction time and tedious work-up, leading to the generation of a large amount of toxic waste. Therefore, there is a need for an efficient method for the synthesis of α-aminonitriles.



Scheme 1.

Recently, we have reported a novel method for the synthesis of α-aminonitriles by catalysis of rhodium(III) iodide hydrate[33] and niobium (V) chloride[34] in acetonitrile. In light of our success in developing several catalytic systems for the synthesis of chiral[35–38] and achiral cyanosilylether[39–43] and Strecker reaction,[33,34] we report a simple method for the synthesis of α-aminonitriles in the presence of thallium(III) chloride tetrahydrate under solvent-free condition at room temperature (r.t.) (Scheme 1). Most recently, our group has developed $TlCl_3{\cdot}4H_2O$ catalyzed acylation of alcohols, phenols and thiols and germinal diacylation of aldehydes under solvent-free conditions.[44]

Although thllium salts are toxic, they are less toxic than lead and mercury. Hence the use of thallium in organic chemistry began in 1970 and it is still in use.[45] Thallium salt can promote a number of reactions, like oxidative and non-oxidative cyclization and aromatic thallation reactions.[46] The three most commonly used thallium salts are thallium acetate, thallium nitrate and thallium trifluroacetate (TTFA). Thallium nitrate has been used as catalyst for oxidative rearrangement of aryl and alkyl ketons to esters,[47] ring contraction of alkylcyclohexanons,[48] synthesis of polyalkylated indol with ring contraction reaction,[49] rearrangement of homoallylic alcohol,[50] ring opening of cyclopropanes[51] and electrophilic cyclization reaction.[52] TTFA has been reported for disulfide bond formation.[53]

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Experimental

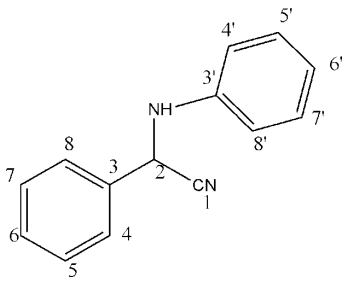
In all cases the ^{1}H NMR (200 MHz) spectra were recorded with a Varian Gemini 2000 spectrometer. Chemical shifts are reported in ppm in $CDCl_3$ with tetramethylsilane as an internal standard. ^{13}C NMR data were collected on a Varian Gemini 2000 spectrometer (100 MHz). GCMS data were recorded with a 1200L single quadrupole GC/MS system with 3800GC/Varian.

General procedure for the synthesis of α-aminonitriles

To a mixture of aldehyde (1 mmol) and amine (1 mmol) were added TMSCN (1.2 mmol) and $TlCl_3 \cdot 4H_2O$ (3.1 mg, 1.0 mol%) at r.t. The completion of the reaction was monitored with TLC and the reaction mixture was diluted with ether. Water (10 ml) was added and the mixture was extracted with ether (3 × 5 ml). The extract was concentrated and the viscous mass was subjected to silica gel flash column chromatography (Silica gel, 4% EtOAc in hexane) to obtain pure α-aminonitrile compound.

The spectral (IR, ^{1}H, ^{13}C NMR, GCMS and HRMS) data of some representative products are given below.

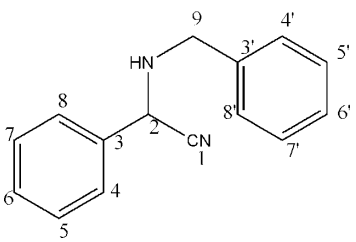
Phenylamino(2-phenyl)acetonitrile (entry 1)



Scheme 2.

White solid, m.p. 75–76 °C; IR (KBr): 3365, 3032, 2950, 2235, 1602, 1501, 1451, 1316, 1267, 933, 752, 693; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.42 (s, 1H), 6.81 (d, J = 8.0 Hz, 2H), 6.98 (t, J = 7.8 Hz, 1H), 7.31 (t, J = 7.8 Hz, 2H), 7.46–7.51 (m, 3H), 7.60–7.64 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 49.88 (C-2), 114.0 (C-4′, 8′), 118.16 (C-1 CN), 119.95 (C-4, 8), 127.04 (C-5, 7), 128.30 (C-6),129.34 (C-6′), 129.97 (C-7′)133.75 (C-3) 144.54 (C-3′); anal. calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.68; H, 5.86; N, 13.49%. GCMS: *m/z* 208 [$M^{+\cdot}$], 181, 92.

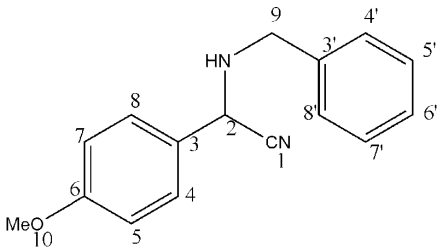
Benzylamino(2-pheny)lacetonitrile (entry 2)



Scheme 3.

Colorless oil; IR (KBr): 3321, 3030, 2227, 1641, 1544, 1419, 1267, 1105, 1027, 921, 825, 749; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.02 (q, J = 13.5 Hz), 4.76 (s, 1H), 7.32–7.46 (m, 8H), 7.59 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 50.91 (C-2), 53.14 (C-9), 118.54 (C-1, CN), 127.06 (C-7, 5), 127.32 (C-5′, 7′), 128.38 (C-4′, 8′), 128.69 (C-8, 4), 128.74 (C-6′), 129.44 (C- 5′), 134.55 (C-3), 137.94 (C-3′); anal. calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 81.10; H, 6.29; N, 12.52%. GCMS: *m/z* 222 [$M^{+\cdot}$], 195, 106, 91.

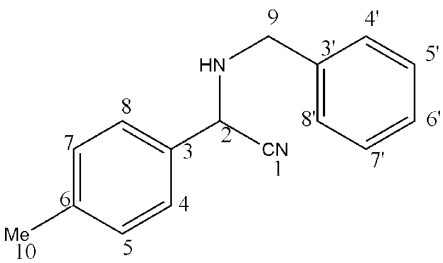
Benzylamino(4-methoxyphenyl)acetonitrile (entry 3)



Scheme 4.

Yellow oil; IR (KBr): 3332, 2930, 2221, 1600, 1503, 1431, 1240, 1018, 930, 754; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.8 (brs, 1H), 3.83 (s, 3H), 4.01 (q, J = 13.2, 2H), 4.72 (s, 1H), 6.92–6.96 (m, 2H), 7.49–7.28 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 51.8 (C-2), 53.4 (C-9), 55.4 (C-10), 114.9 (C-7), 119.4 (C-1 CN), 127.4 (C-7′, 5′), 128.2 (C-6′), 128.9 (C-5), 129.5 (4′ 8′), 132.5 (C-8, 4), 138.9 (C-3), 145.2 (C-3′), 159.8 (C-6); anal. calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.24; H, 6.48; N, 11.14%. GCMS: *m/z* 252 [$M^{+\cdot}$].

Benzylamino(2-tolyl)acetonitrile (entry 4)

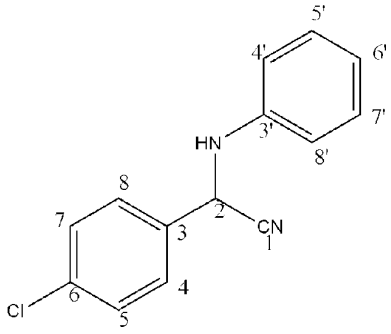


Scheme 5.

Colorless oil; IR (KBr): 3324, 3029, 2227, 1580, 1495, 1219, 1022, 919, 772, 696; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.82 (brs, 1H), 2.38 (s, 3H), 4.01 (q, J = 13.2 Hz, 2H), 4.72 (s, 1H), 7.21 (d, J = 8.0 Hz, 2H), 7.28–7.45 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.12 (C-10), 51.21 (C-2), 53.19 (C-9), 118.86 (C-1, CN), 127.19 (C-5′, 7′), 127.59 (C-5, 7), 128.39 (C-5′, 7′), 128.60 (C-8, 4), 129.60 (C-3), 136.71 (C-6), 138.97 (C-3′); anal. calcd for $C_{16}H_{16}N_2$: C, 81.32; H, 6.82; N, 11.85. Found: C, 81.27; H, 6.72; N, 11.54%. GCMS: *m/z* 236 [$M^{+\cdot}$], 209 [-HCN], 91.

Phenylamin (4-chlorophenyl)acetonitrile (entry 5)

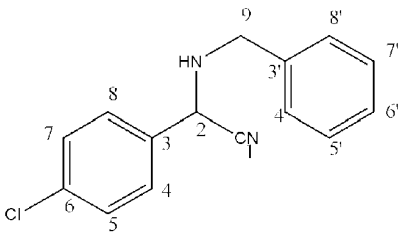
White solid, m.p. 108–110 °C; IR (KBr): 3405, 2928, 2232, 1609, 1522, 1458, 1260, 1080, 782; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.09 (brs, 1H), 5.41 (s, 1H), 6.76 (d, J = 8.0 Hz, 2H), 6.93 (t, J = 7.8 Hz, 1H), 7.26–7.30 (m, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 49.54 (C-2), 114.25 (C-1, CN), 117.81



Scheme 6.

(C-8′ 4′), 120.47 (C-4′, 8′), 128.51 (C-7, 5), 129.24 (C-5′, 7′), 129.54 (C-8, 4), 132.90 (C-3), 135.49 (C-6), 144.32 (C-3′); anal. calcd for $C_{14}H_{11}ClN_2$: C, 69.28; H, 4.57; Cl, 14.61; N, 11.54. Found: C, 69.14; H, 4.28; Cl, 14.32; N, 11.34%. GCMS: *m/z* 242 [$M^{+\cdot}$].

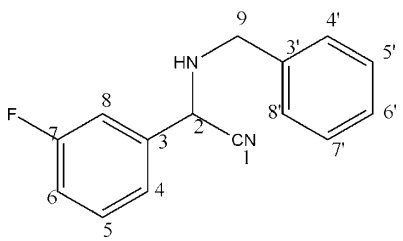
Benzylamino(4-chlorophenyl)acetonitrile (entry 6)



Scheme 7.

Light yellow oil; IR (KBr): 3340, 2929, 2227, 1598, 1490, 1221, 1067, 919, 770, 691; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.97 (brs, 1H), 4.02 (q, J = 13.3, 2H), 4.75 (s, 1H), 7.54–7.34 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 51.47 (C-2), 53.0 (C-9), 118.52 (C-1, CN), 127.91 (C-7′, 5′), 128.56 (C-7, 5), 128.85 (C-8′, 4′), 129.30 (C-8, 4), 133.39 (C- 3), 135.18 (C-6), 138.02 (C-3′); anal. calcd for $C_{15}H_{13}ClN_2$: C, 70.18; H, 5.10; Cl, 13.81; N, 10.91. Found: C, 70.29; H, 5.48; Cl, 13.58; N, 10.44%. GCMS: *m/z* 256 [$M^{+\cdot}$].

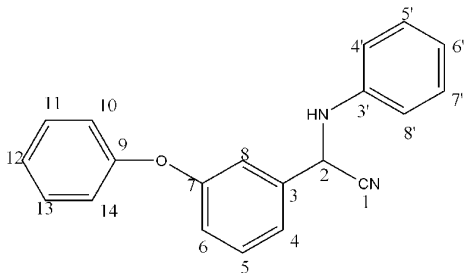
Benzylamino(3-fluorophenyl)acetonitrile (entry 9)



Scheme 8.

Colorless oil; IR (KBr): 3325, 3030, 2230, 1614, 1592, 1487, 1243, 1139, 1075, 964, 771, 699; ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.02 (q, 2H, J = 13.0 Hz), 4.77 (s, 1H), 7.11 (d, 1H, J = 8.0 Hz), 7.30–7.46 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) = 51.0 (C-2), 52.7 (C-9), 114.5 (C-6), 116.0 (C-8), 118.1 (C-1 CN), 122.7 (C-4), 127.6 (C-6′), 128.2 (C-4′, 8′), 128.5 (C-5′, 7′), 130.3 (C-5), 137.0 (C-3), 137.7 (C-3′), 164.0 (C-7); anal. calcd for $C_{15}H_{13}FN$: C, 74.98; H, 5.45; F, 7.91; N, 11.66. Found: C, 74.37; H, 5.58; F, 7. 78; N, 11.49%. GCMS: *m/z* 240 [$M^{+\cdot}$], 107, 105, 91; HRMS calcd for $C_{15}H_{13}FN_2$: 240.1063. Found: 240.1062.

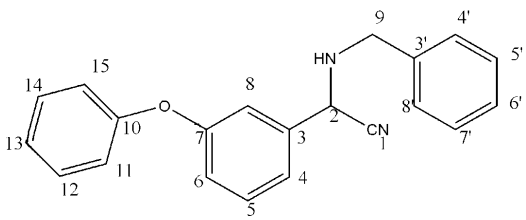
Phenylamino (3-phenoxyphenyl) acetonitrile (entry 10)



Scheme 9.

Yellow solid, m.p. 64–66 °C; IR (KBr): 3375, 3037, 2923, 2230, 1602, 1499, 1456, 1250, 1219, 1163, 1023, 967, 751, 692; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.79 (brs, 1H), 5.39 (s, 1H), 6.68–6.84 (m, 2H), 6.92 (t, J = 7.6 Hz, 1H), 7.06–7.48 (m, 11H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 49.75 (C-2), 114.14 (C-8′, 4′), 115.06 (C-6′), 117.25 (C-1 CN), 118.48 (C-10), 118.98 (C-11), 120.20 (C-13), 121.49 (C-5′), 123.86 (C-7′), 129.42 (C-12), 129.87 (C-14), 130.57 (C-4′, 8′), 135.74 (C-3), 144.39 (C-3′), 156.15 (C-7), 158.11 (C-9); anal. calcd for $C_{20}H_{16}N_2O$: C, 79.98; H, 5.37; N, 9.33. Found: C, 79.74; H, 5.52; N, 9.44%. GCMS: *m/z* 300 [$M^{+\cdot}$], 273.

Benzylamino(3-phenoxyphenyl)acetonitrile (entry 11)

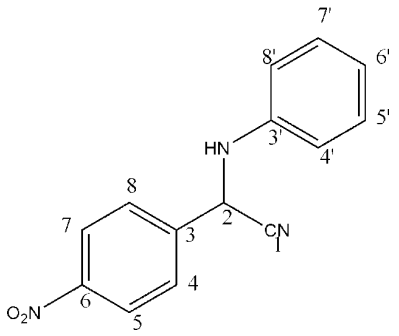


Scheme 10.

Light yellow oil; IR (KBr): 3365, 3029, 2925, 2226, 1580, 1440, 1106, 1019, 825, 753, 692; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.3 (brs, 1H, NH), 4.03 (q, 2H, J = 13.4 Hz), 4.76 (s, 1H), 7.05–7.13 (m, 2H), 7.22–7.47 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) = 50.8 (C-2), 52.8 (C-9), 117.3 (C-8), 118.2 (C-1 CN), 118.7 (C-6), 118.9 (C-11, 15), 121.5 (C-4), 123.4 (C-13), 127.3 (C-6′), 128.0 (C-4′, 8′), 128.0 (C-5), 129.6 (C-11, 14), 129.9 (C-5′, 7′), 136.4 (C-3), 137.7 (C-3′), 156.2 (C-7), 157.5 (C-10); anal. calcd for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.64; H, 5.28; N, 8.34%. GCMS: *m/z* 315 [M + H], 314 [$M^{+\cdot}$]; HRMS calcd for $C_{21}H_{18}N_2O$: 314.1419. Found: 314.1418.

Phenylamino(4-nitrophenyl)acetonitrile (entry 12)

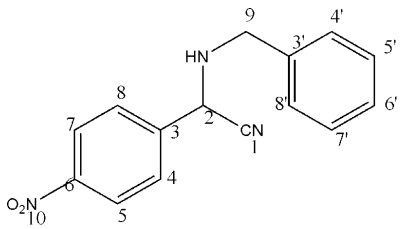
Viscous liquid; IR (KBr): 3422, 2923, 2235, 1597, 1515, 791; ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.08 (d, 1H, J = 8.0 Hz), 5.37 (d, 1H, J = 8.0 Hz), 6.80 9d, 2H, J = 8.0 Hz), 6.91 (t, 1H, J = 7.9 Hz) 7.20 (t, 2H, J = 7.9 Hz), 7.70 (d, 2H, 8.1 Hz), 8.10 (d, 2H, J = 8.1 Hz); ^{13}C NMR



Scheme 11.

($CDCl_3$, 100 MHz): δ 49.8 (C-2), 115.3 (C-8′, 4′), 118.0 (C-1 CN), 127.0 (C-8, 4), 127.9 (C-4, 8), 127.6 (C-7, 5), 128.5 (5′, 7′), 129.0 (C-6′), 133.8 (C-4), 144.1 (C-3), 145.0 (C-6); anal. calcd for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.51; H, 4.73; N, 16.21%. GCMS: *m/z* 253 [$M^{+\cdot}$], 227.

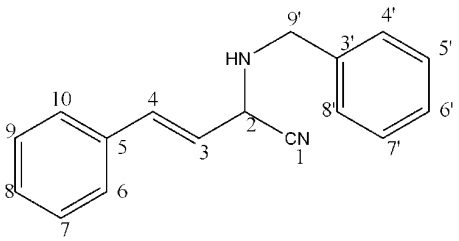
Benzylamino(4-nitrophenyl)acetonitrile (entry 13)



Scheme 12.

Brown oil; IR (KBR): 3421, 2922, 2234, 1600, 1480, 1079, 692; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.80 (brs, 1H, NH), 3.92 (q, 2H, J = 13.3 Hz), 4.71 (s, 1H), 7.20–7.60 (m, 5H), 8.0 (d, 2H, J = 8.0 Hz), 8.31 (d, 2H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 49.8 (C-2), 51.34 (C-9), 115.3 (C-8′, 4′), 118.0 (C-1 CN), 127.0 (C-8, 4), 127.9 (C-4, 8), 127.3 (C-7, 5), 128.5 (5′, 7′), 129.0 (C-6′), 133.8 (C-4), 144.1 (C-3), 145.0 (C-6); anal. calcd for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.11; H, 4.39; N, 15.61%. GCMS: *m/z* 253 [$M^{+\cdot}$], 227. GCMS: *m/z* 267 [$M^{+\cdot}$].

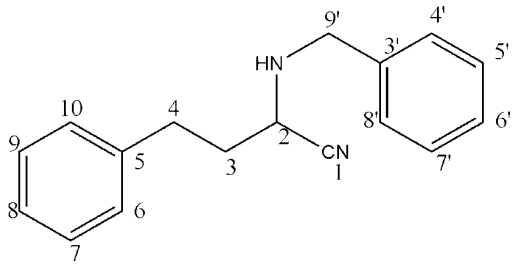
(E)Benzylamino-4-phenylbut-3-enenitrile (entry 14)



Scheme 13.

Brown oil; IR (KBr): 3260, 3010, 2220, 1600, 1499, 1219, 772; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.70 (brs, 1H, NH), 4.08 (q, 2H, J = 13.5 Hz), 4.40 (m, 1H), 6.28 (dd, 1H, J = 6.0, 17.0 Hz), 6.93 (d, 1H, J = 2.0, 16.8 Hz), 7.30–7.44 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 49.8 (C-2), 50.9 (C-9′), 118.0 (C-1 CN), 122.3 (C-3), 127.0 (C-8), 127.3 (C-6′), 127.9 (4′, 8′), 128.3 (C-10, 6), 128.5 (5′, 7′), 129.0 (C-9, 7), 133.8 (C-4), 135.1 (C-5), 138.0 (C-3′); anal. calcd for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28. Found: C, 82.34; H, 6.39; N, 11.37%. GCMS: *m/z* 248 [$M^{+\cdot}$], 157, 90.

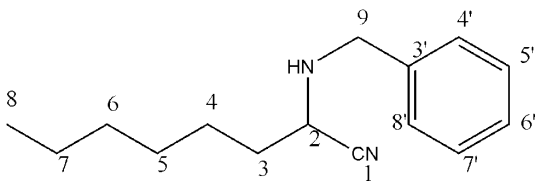
Benzylamino(4-phenyl)butanenitrile (entry 15)



Scheme 14.

Colorless oil; IR (KBr): 3318, 2225, 1736, 1496, 1454, 1244; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.06–2.19 (m, 3H), 2.88 (t, J = 2.0 Hz), 3.47–3.54 (m, 1H), 3.97 (q, J = 13.2 Hz, 2H), 7.19–7.41 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 31.65 (C-4), 35.05 (C-3), 48.90 (C-2) 51.56 (C-9′), 119.97 (C-1), 126.25 (C-6′), 127.40 (C-8), 128.11 (C-10, 6), 128.22 (C-9, 7), 128.41 (C-4′, 8′), 128.45 (5′, 7′), 138.15 (C-3′), 139.74 (C-5); anal. calcd for $C_{17}H_{18}N_2$: C, 81.56; H, 7.25; N, 11.19. Found: C, 81.83; H, 7.78; N, 11.43%. GCMS: *m/z* 250 [$M^{+\cdot}$], 160.

Benzylamino-octanenitrile (entry 16)



Scheme 15.

Brown oil; IR (KBr): 3321, 3030, 2928, 2857, 2220, 1453, 1219, 1132, 1028, 772, 698; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.84 (t, J = 7.8 Hz, 3H), 1.21–1.44 (m, 8H), 1.66 (q, J = 7.1 Hz, 2H), 2.04 (brs, 1H), 3.40 (t, J = 7.8 Hz, 1H), 3.77 (q, J = 13.2 Hz, 2H), 7.20–7.28 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) = 13.97 (C-8), 22.38 (H-7), 25.47 (C-4), 28.57 (C-5), 31.41 (C-6), 33.42 (C-3), 49.65 (C-2), 51.53 (C-9), 120.21 (C-1 CN), 127.10 (C-6′), 127.66 (C-4′, 8′), 128.24 (C-5′, 7′), 138.32 (C-3′); anal. calcd for $C_{15}H_{22}N_2$: C, 78.21; H, 9.63; N, 12.16. Found: C, 78.77; H, 9.68; N, 12.46%. GCMS: *m/z* 230 [$M^{+\cdot}$], 203.

Results and Discussions

The catalytic activity of $TlCl_3{\cdot}4H_2O$ was tested using benzaldehyde as a model substrate. $TlCl_3{\cdot}4H_2O$ exhibited excellent activity under solvent-free conditions. When a mixture of benzaldehyde (1 mmol), benzyl amine (1 mmol) and TMSCN (1.2 mmol) was treated with various amounts of $TlCl_3{\cdot}4H_2O$ (0.1–5.0 mol%) at r.t., the formation of α-aminonitriles occurs in relatively short reaction time. The catalyst loading up to 0.1 and 0.5 mol% gives a

Table 1. Three component synthesis of α-aminonitriles under various conditions[a]

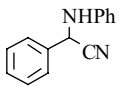
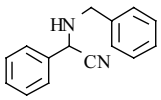
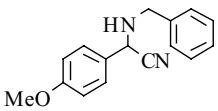
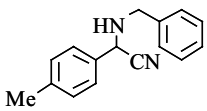
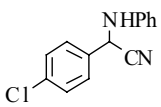
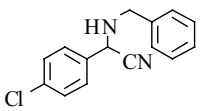
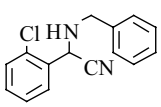
Entry	Catalyst (mol%)	Solvent	Time (min)	Yield (%)[b]
1	0.1	–	25	86
2	0.5	–	25	91
3	1.0	–	15	96
4	2.0	–	15	98
5	5.0	–	15	98
6	1.0	CH_3CN	15	95
7	1.0	THF	1h	90
8	1.0	CH_2Cl_2	1h	88

[a] $TlCl_3{\cdot}4H_2O$ was added to a mixture of 1 mmol of benzaldehyde, 1 mmol of benzyl amine and 1.2 mmol of TMSCN.
[b] Isolated yield.

lower yield of α-aminonitriles for a longer reaction period (Table 1, entries 1 and 2). With 1 mol% catalyst the yield was increased and afforded the corresponding α-aminonitriles in 96% yield within 15 min under solvent-free condition (entry 3). The reactions give a similar yield with larger quantities of catalyst (Table 1, entries 4 and 5). It was observed that 1 mol% catalyst in the presence of solvent CH_3CN also gave the corresponding α-aminonitriles in 95% yield within 15 min (entry 6), whereas THF and CH_2Cl_2 took longer to complete the reaction and the yield was somewhat reduced (entries 7 and 8). Thus 1 mol% of $TlCl_3{\cdot}4H_2O$ proved to be the optimal amount for the synthesis of α-aminonitriles at r.t. under solvent-free conditions (Table 1, entry 3).

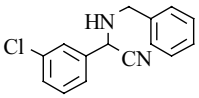
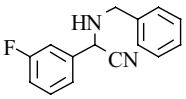
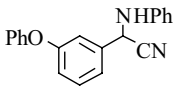
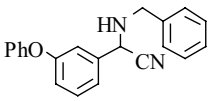
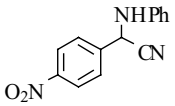
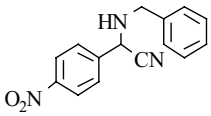
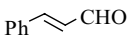
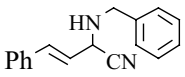
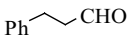
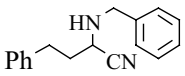
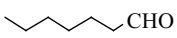
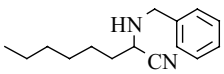
A variety of aldehydes and amines were coupled with TMSCN in the presence of a catalytic amount of $TlCl_3{\cdot}4H_2O$ in solvent-free conditions at r.t. The reactions proceeded smoothly to afford the corresponding α-aminonitriles in high yields in short reaction times (Table 2). This method is equally effective with aldehydes bearing electron-donating and weakly electron-withdrawing substituents in the aromatic ring of aldehydes and amines as well. The reactions of *p*-methoxybenzaldehyde and *p*-tolualdehyde with benzylamine were completed in 15 and 18 min with 95 and 92% yields, respectively (entries 3 and 4). The reaction of *p*-chlorobenzaldehyde both with aniline and with benzylamine took place in 15 min with 95 and 94% yields, respectively (entries 5 and 6). The reaction of *o*-chlorobenzaldehyde and *m*-chlorobenzaldehyde with benzylamine gave a good result in 15 min, 93 and 94% yields, respectively (entries 7 and 8). *o*-Chlorobenzaldehyde showed no steric effect at all. *m*-Fluorobenzaldehyde gave a 96% yield in 12 min (entry 9). *m*-Phenoxybenzaldehyde took 15 min to complete the reaction with aniline and benzylamine to obtain 96 and 97% yields, respectively (entries 10 and 11). The reactions of 4-nitrobenzaldehyde with aniline and benzylamine also proceeded nicely within 20 and 15 min with 92 and 90% yields, respectively (entries 12 and 13). It should be noted that the reaction of 4-nitrobenzaldehyde and

Table 2. $TlCl_3{\cdot}4H_2O$ catalyzed three component synthesis of α-aminonitriles[a]

Entry	Aldehyde	Amine	Product	Time (min)	Yield (%)[b]
1	C_6H_5CHO	$C_6H_5NH_2$		15	94
2	C_6H_5CHO	$PhCH_2NH_2$		15	96
3	4-$MeOC_6H_4CHO$	$PhCH_2NH_2$		15	95
4	4-MeC_6H_4CHO	$PhCH_2NH_2$		18	92
5	4-ClC_6H_4CHO	$C_6H_5NH_2$		15	95
6	4-ClC_6H_4CHO	$PhCH_2NH_2$		15	94
7	2-ClC_6H_4CHO	$PhCH_2NH_2$		15	93

(*continued overleaf*)

Table 2. (*Continued*)

Entry	Aldehyde	Amine	Product	Time (min)	Yield (%)[b]
8	3-ClC_6H_4CHO	$PhCH_2NH_2$		15	94
9	3-FC_6H_4CHO	$PhCH_2NH_2$		12	96
10	3-$PhOC_6H_4CHO$	$C_6H_5NH_2$		15	96
11	3-$PhOC_6H_4CHO$	$PhCH_2NH_2$		15	97
12	4-$NO_2C_2H_4CHO$	$C_6H_5NH_2$		20	92[c]
13	4-$NO_2C_2H_4CHO$	$PhCH_2NH_2$		15	90[c]
14		$PhCH_2NH_2$		15	98
15		$PhCH_2NH_2$		15	99
16		$PhCH_2NH_2$		20	88

[a] The structure of the products were settled from spectral (IR, ^1H, ^{13}C NMR and GCMS) data. The spectral data (IR, ^1H, ^{13}C NMR) of the compounds were compared with the literature values.[11,12]
[b] Isolated yield.
[c] Reactions of 4-nitrobenzaldehyde was carried out in the presence of solvent CH_3CN.

aniline or benzyl amine should be carried out in the presence of acetonotrile as a solvent because without solvent there was only a 50–60% reaction conversion observed, even after stirring 1h at r.t. The 4-nitro group hardly exhibited an electronic effect on the reaction. It was observed that the reaction with cinnamaldehyde gave a 98% yield of the corresponding aminocyano compound in 15 min (entry 14), whereas hydrocinnamaldehyde gave 99% yield in the same duration of reaction (entry 15). The reaction of heptaldehyde gave the corresponding product at 88% yield (entry 16). Acid-sensitive aldehydes such as cinnamaldehyde produce the aminocyano compound in good yield. This may indicate that the catalytic system selectively activates the carbonyl function and keeps the double bond of cinnamaldehyde intact. This method does not require any additives to promote the reaction. No cyanohydrin trimethylsilyl ethers (an adduct between an aldehyde and trimethylsilylcyanide) were obtained under these reaction conditions because of the rapid formation of the imine intermediate by catalytic action of $TlCl_3{\cdot}4H_2O$. In contrast to our reaction time and low catalyst loading (1 mol%) in solvent-free condition, 5–10 h is required in the presence of 10 mol% of $BiCl_3$.[19] With montmorillonite KSF clay as a catalyst,[23] 3.0–5.5 h is taken for completion of the reaction in presence of 1.0 g clay. A reaction time of 1–8 h and 20 mol% I_2[24] are necessary for completion of the reaction. Recently a method utilizing 5 mol% $Fe(Cp)_2$ PF_6 was reported where 20 min were needed for the synthesis of α-aminonitriles.[32]

Conclusion

In conclusion, we have found that thallium (III) chloride is a highly efficient catalyst for synthesis of α-aminonitriles through the three-component coupling reaction of aldehydes, amines and TMSCN under solvent-free conditions at r.t. Both aromatic and aliphatic aldehydes afford excellent yields of product. The important features of our method are: short reaction time, low catalyst loading (1 mol%), air-stable and mild reaction conditions, simple work-up, and inexpensive and readily available catalyst. Studies concerning the asymmetric reaction as well as the application of the thallium (III) chloride in the synthesis of chiral α-aminonitriles and other organic transformations are in progress.

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